Clinical Measurement of GFR in Chronic Renal Failure

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Objectives

- Know the limitations of serum creatinine as a marker for GFR (glomerular filtration rate), and alternatives for measuring GFR
- Know the commonly used radioisotope measures of GFR, their indications, and their limitations
- Know the changes that occur with GFR with normal aging
- Know the formulas used to approximate GFR from serum creatinine and their limits

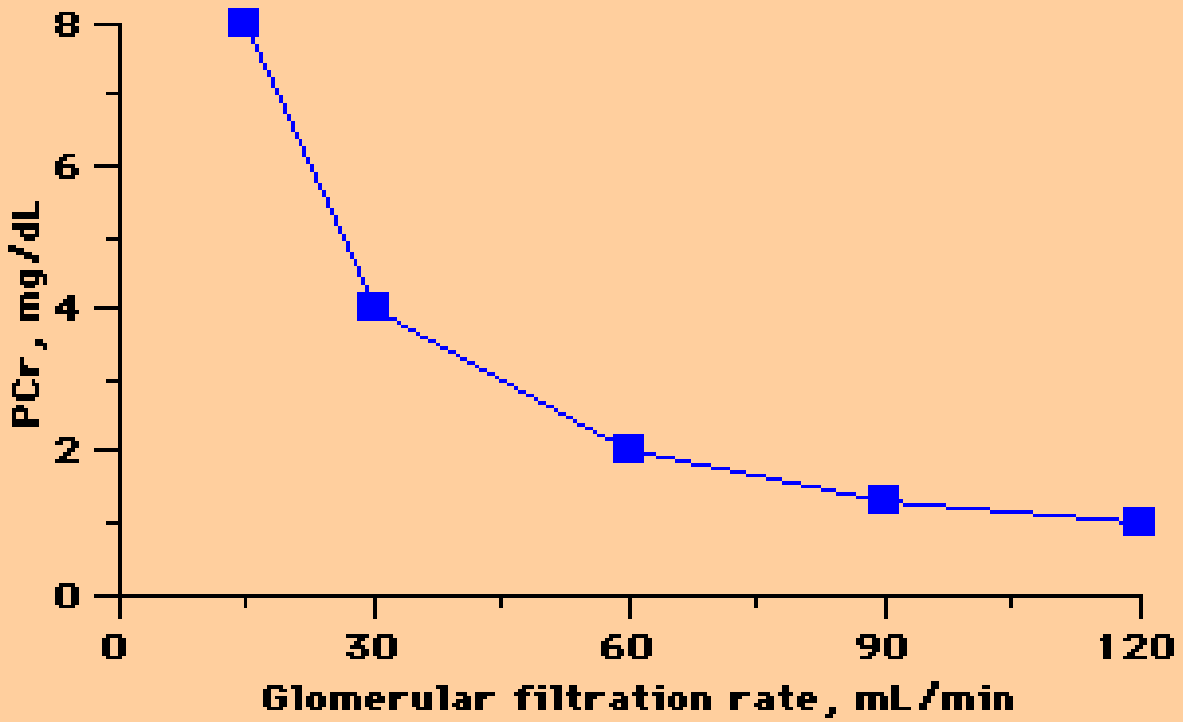
Background

- Serum creatinine can be a misleading indicator of GFR, especially in the elderly, women, or in malnourished patients.
- Severe renal insufficiency often goes undetected because serum creatinine does not exceed certain arbitrary thresholds, despite a low GFR.

Background (Cont'd)

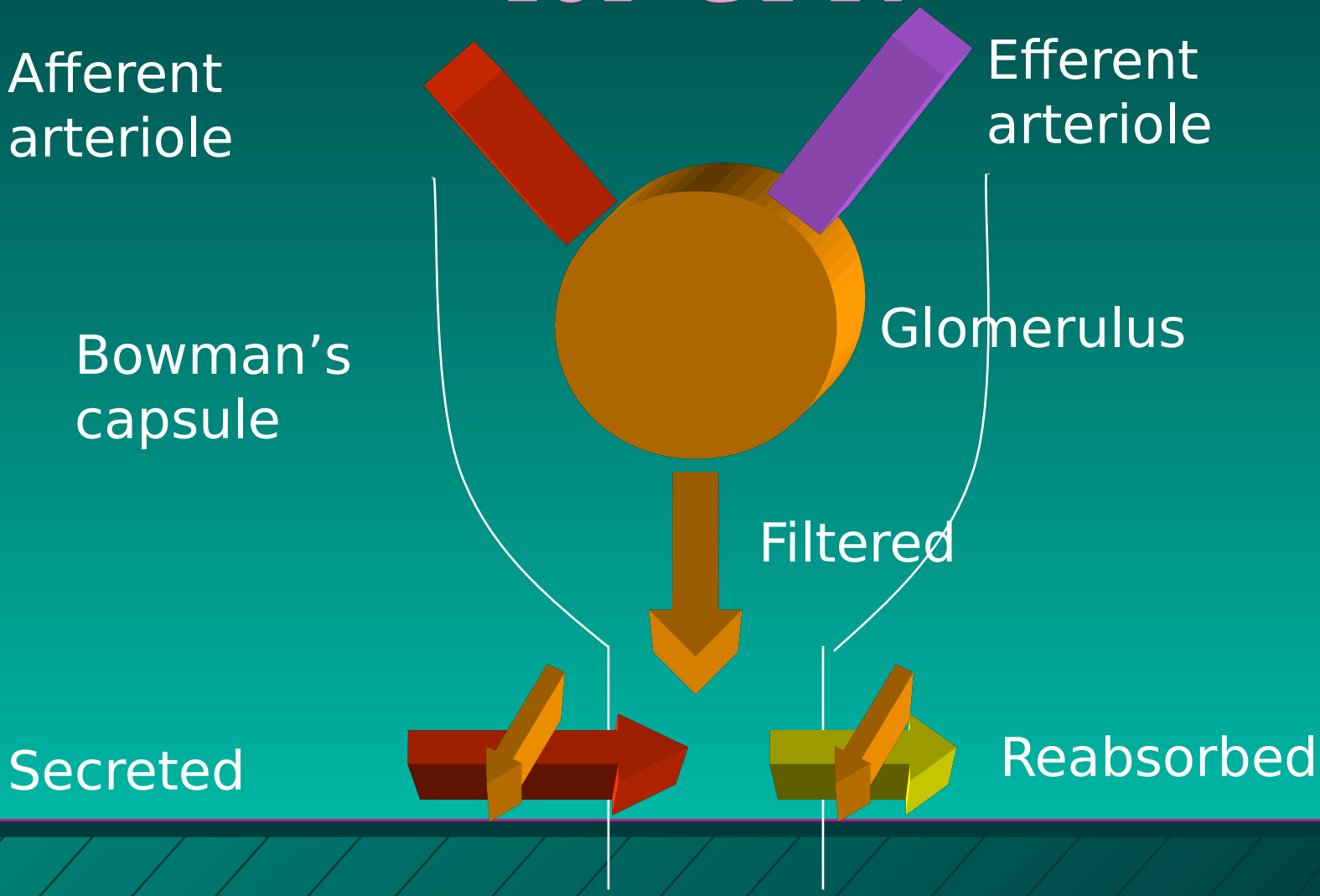
- Planning for the treatment of end stage renal disease, and even referral to nephrology, is often hampered by this approach.
- What is the best, most practical way to assess GFR and if possible trace the course of progression of chronic renal disease?

Plasma creatinine and GFR

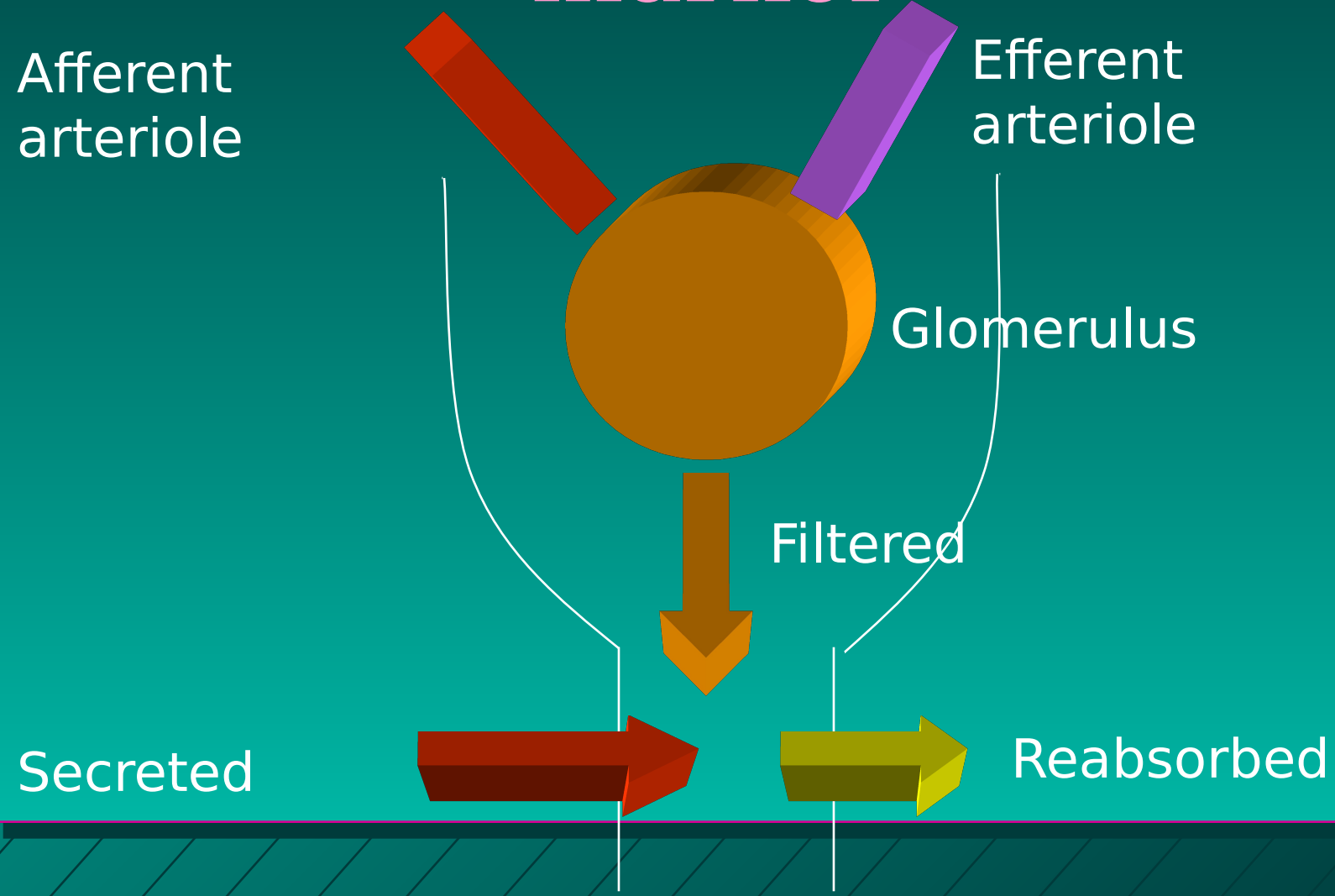


Plasma creatinine and GFR Idealized steady-state relationship between the plasma creatinine concentration (PCr) and the GFR. A fall in GFR decreases creatinine filtration and produces a proportionate rise in the plasma creatinine concentration.

Inulin: the perfect marker for GFR



Creatinine: an imperfect marker



Practical measurement of GFR

- Clinical medicine has pursued a practical alternative to inulin for the determination of GFR in daily management.
- Alternatives have predominantly consisted of:
  - **Radioisotope studies**
  - **estimations of GFR based on serum creatinine, either**
    - **using agents that block tubular secretion of creatinine**
    - **or incorporating age, weight, +/- height, and gender, since these all impact GFR independently of serum creatinine**

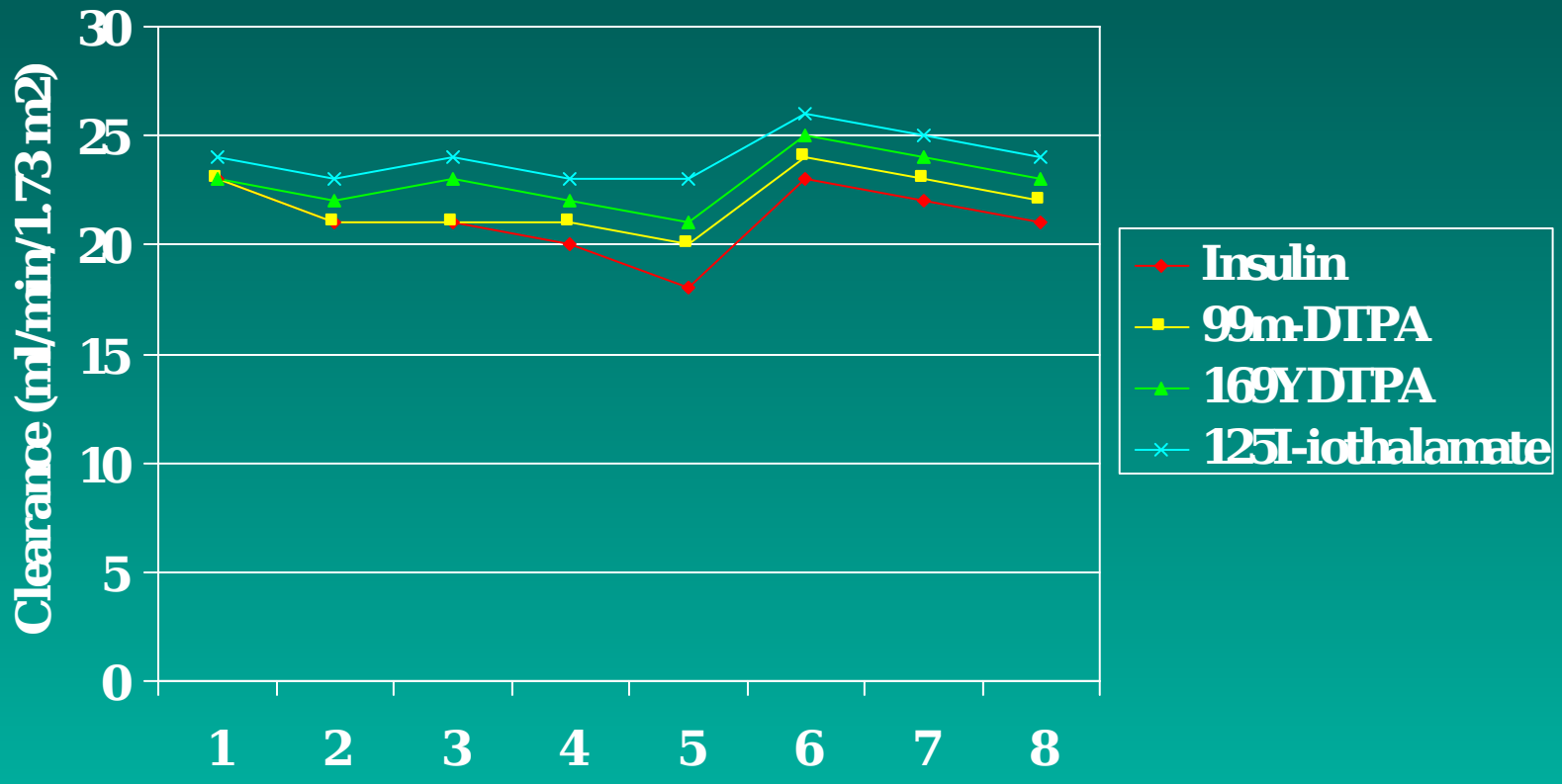
Radioisotope measurement of GFR

Study	N (male, female)	Agent	Compared to:
Gaspari, Moscovi, et al	19 (13, 6) CrCl 5-178 (varied diagnoses)	Nonradioactive iothalamate	51Cr-EDTA
Choyke P, Austin H, Frash et al	90 (genders not mentioned), CyA Tx for varied diagnoses (uveitis, MS, MGN) GFR 15-147	Gadolinium-DTPA	99mTC-DTPA
Rocco, Buckalew, Moore	41, GFR 10-118	Nonradioactive Iohexol	Iothalamate
Wharton, Sudeen et al	18 ICU patients with varied diagnoses, GFR 2-69	99mTC-DTPA	Inulin and ClCr

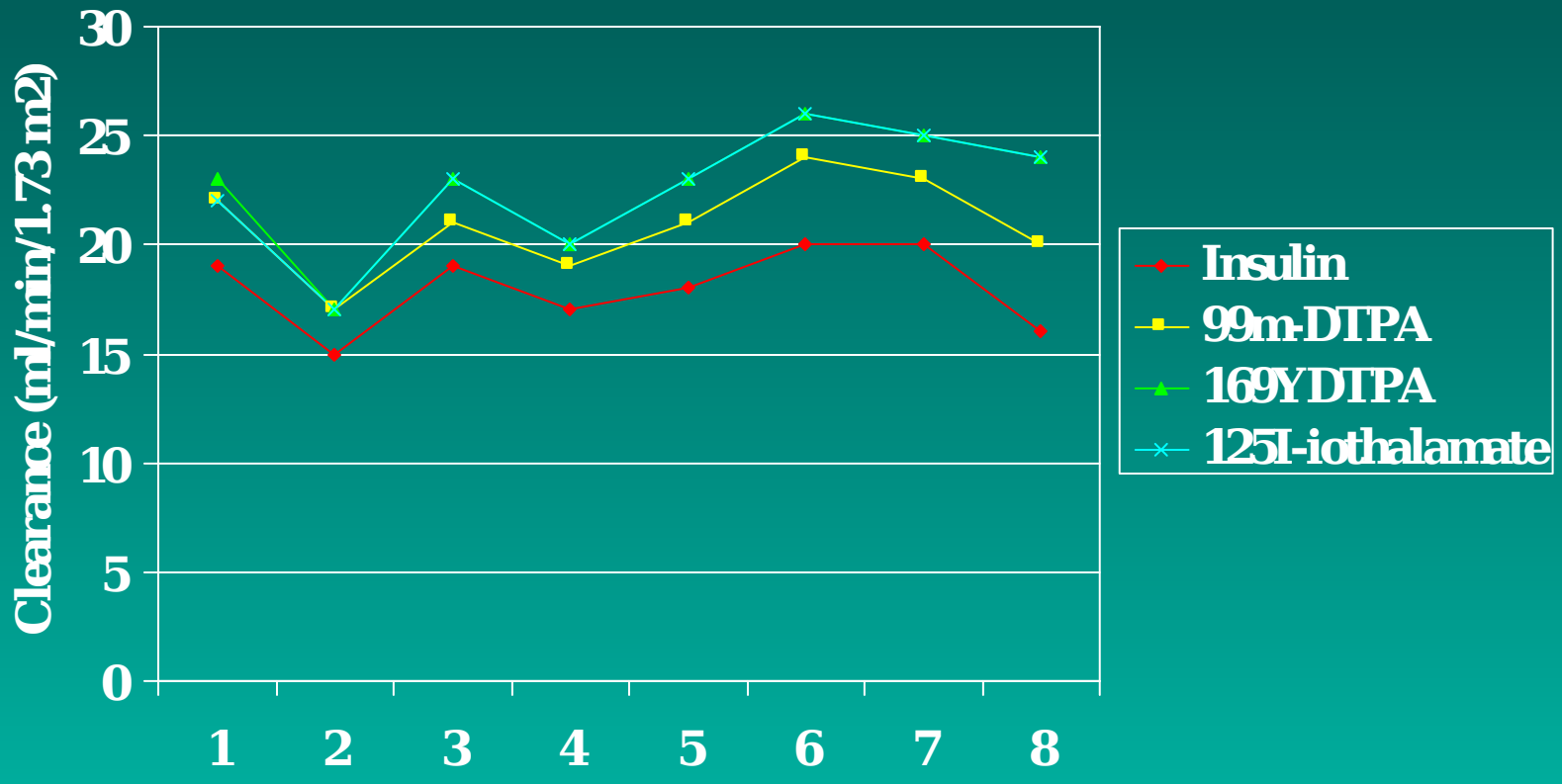
Comparison of isotopic markers with inulin

- Perrone RD, Steinman TI, Beck GJ, et al. Am J Kid Dis 16(3);224-235, 1990.
- The only prospective study that has compared various radiopharmaceuticals against each other and inulin
- 16 nonedematous paid volunteers with Scr>1.5 mg/dl, considered for Phase II of MDRD but excluded because of lack of progression of CRI
- Four additional healthy volunteers

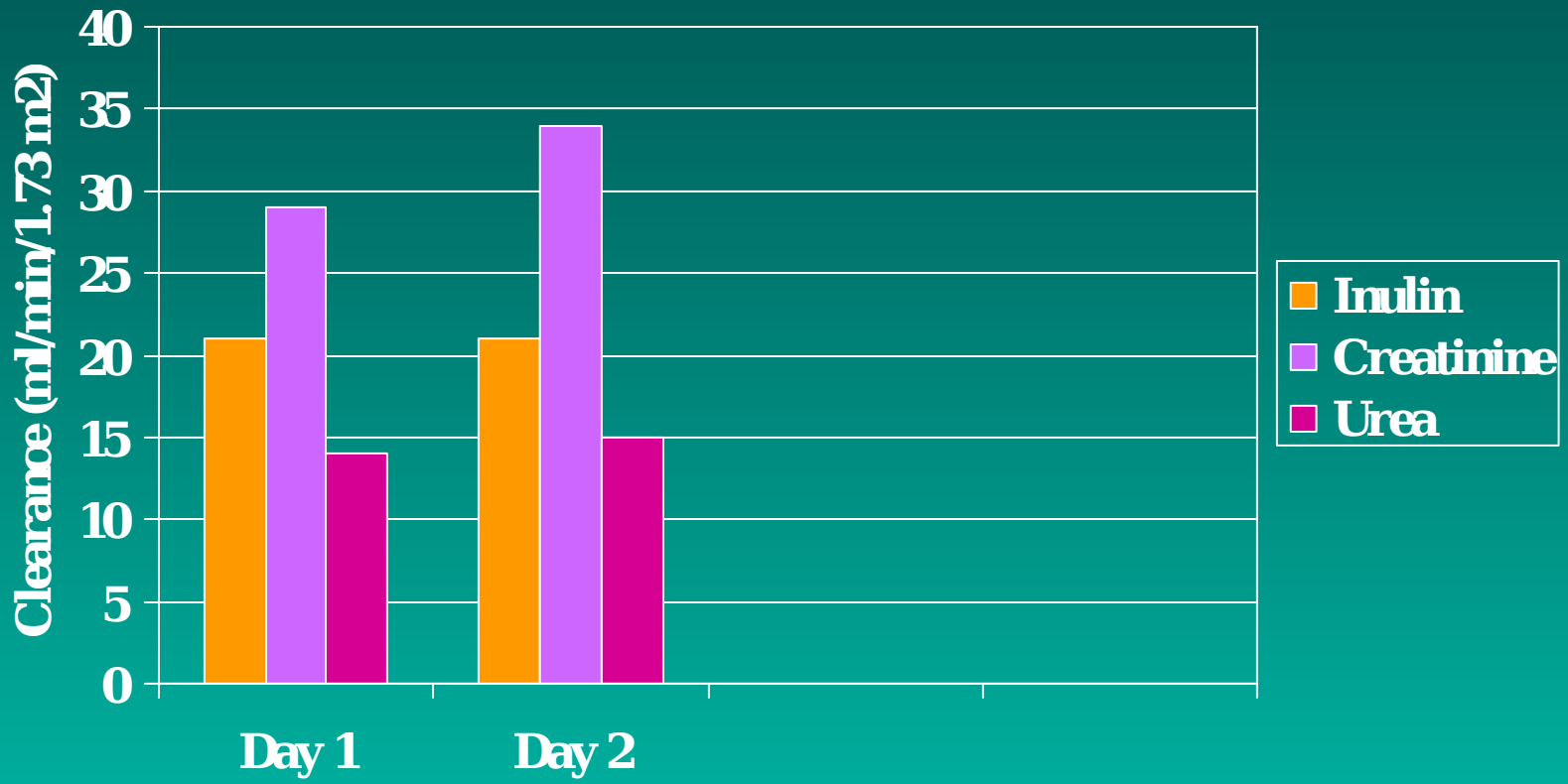
Comparison or isotopic markers with inulin (Day I)



Comparison or isotopic markers with inulin (Day 2)



Inulin vs. creatinine and urea clearances



See Notes Below

Inulin vs. creatinine and urea clearances (cont'd)

- Inulin clearance is fairly close to the average of the urea and creatinine clearances, given the limitations of 24 hour urine collections.
- However, this average is only a coincidence and has no physiologic reason or significance. Its reproducibility against inulin in large populations is untested.

Inulin vs. creatinine and urea clearances (cont'd)

- Creatinine clearance significantly overestimated inulin clearance in this population, and urea clearance underestimated it, but not always by a proportional or reproducible amount. Even in excellent conditions (1) 24 hour urine collections are unreliable (either overcollections or undercollections) about 16% of the time.

Tubular secretion blocking agents

- Since cimetidine is known to block the tubular secretion of creatinine, several studies have looked at using this medication to produce a reliable GFR.
- One of the more recent studies is presented on the next slide.

Use of single dose oral cimetidine in estimation of GFR

- Studied 17 renal transplant patients with CRI (SCR 2-7 mg/dl) with 3-hour timed urine specimens after a single dose of 800 mg oral cimetidine (TCC) compared to ^{125}I-iothalamate GFR (Ciothal).
- Also performed 13 conventional CrCl (TC).
- Zaltzman JS, Whiteside C, Cattran DC, Lopea FM, Logan AG. Accurate measurement of impaired glomerular filtration using single dose oral cimetidine. Am J Kidney Dis 1996;27(4):504-511

Use of single dose oral cimetidine in estimation of GFR

- R^2 of TCC with Ciothal was 0.95.
- R^2 of TC with Ciothal was 0.89 ($P<0.001$).
- Power analysis was not performed in study but was close to 1.00 for comparison of TCC with Ciothal, indicating 17 patients was sufficient sample size to avoid type II error.

Use of single dose oral cimetidine in estimation of GFR

- Variability was low and reproducibility was high.
- Protocol is on next slide.

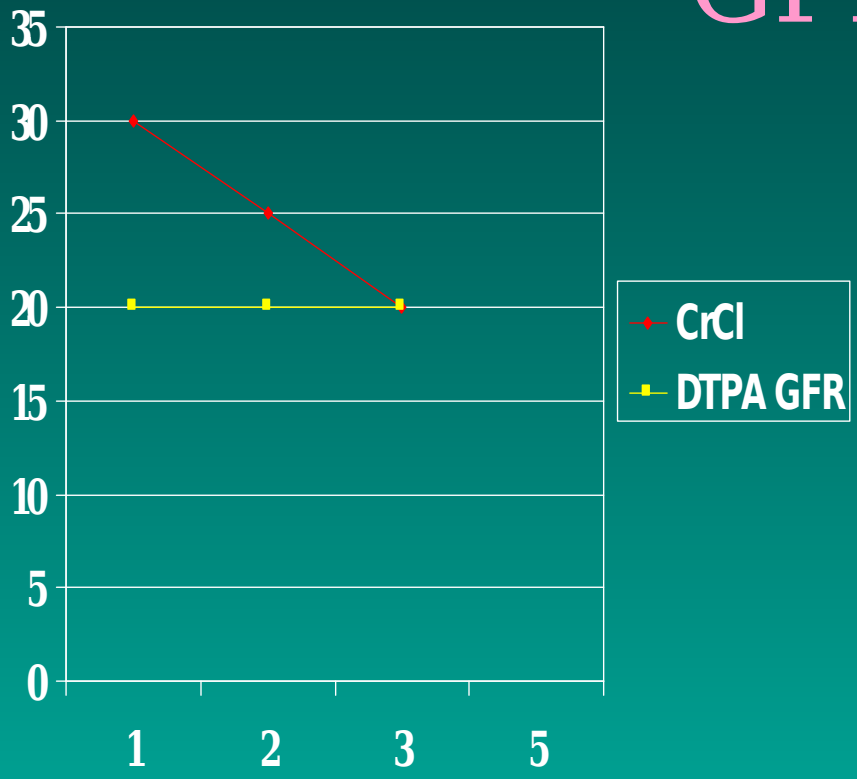
Cimetidine GFR protocol

- Low protein breakfast (0.2 mg/kg) or fast for morning test. Obtain height and weight.
- 800 mg oral cimetidine with 1 L water. Void.
- Allow one hour equilibration
- After one hour, complete void, ensure at least 3 cc/min (180 cc), replace urine volume with equal volume of water
- Begin 3-hour timed urine collection, replacing urine with water in equal volume
- Obtain mid-point (1.5 hour) serum creatinine
- Calculate timed creatinine clearance, ClCr=Vol*Ucr/Scr*time. Correct for body surface area.
- ***Bottom line: still fairly complicated, but should be considered in selected cases.***

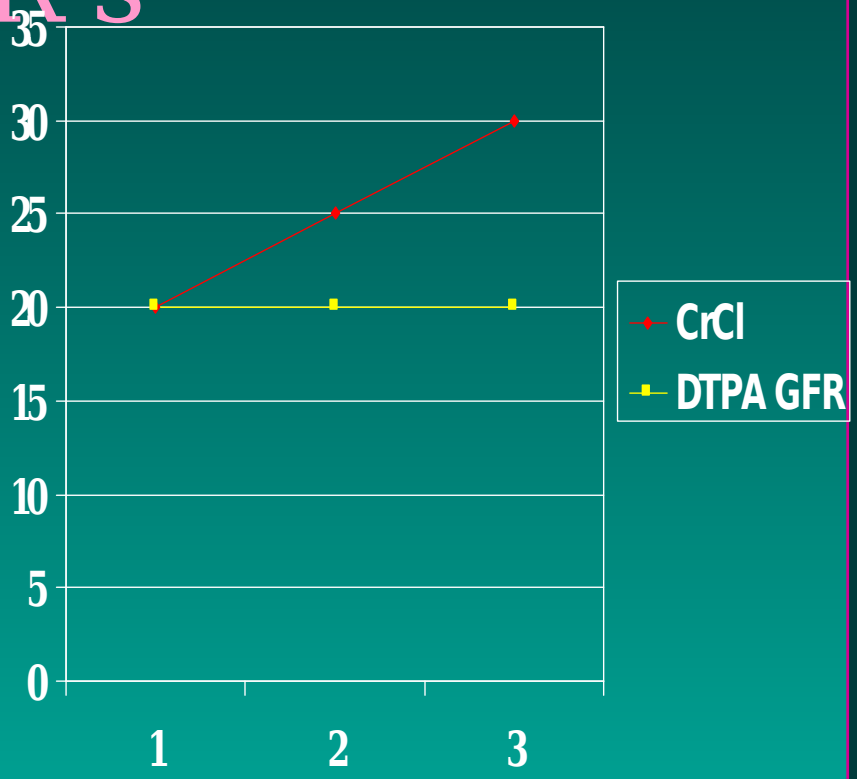
Progression of CRI based on creatinine clearance

- Walser M, Drew HH, LaFrance ND. Creatinine measurements often yield false estimates of progression in chronic renal failure. Kid Int 1988;34:412-418
- Followed 17 patients with CRF (GFR 4-23 cc/min/1.73 m2) for a mean of 15 months.
- In over half of patients followed, there was no clear correlation between CrCl and 99Tm-DTPA GFR.

Sequential CrCl and isotope GFR's



Patient One



Patient Two

Estimation of GFR from serum creatinine only

- Many formulations have attempted to predict GFR from a serum creatinine measurement only, most factoring in age, weight/height, and gender, which are all independent of serum creatinine in influencing GFR.
- This would be the easiest approach clinically
- A table of the selected studies follows.

Estimations of GFR from serum creatinine

Study	*N (male, female)*	*Avg Age*	*Population*	*Study Design*	*Comparison*
Cockroft, Gault	249 (239,10: 96% male), 100% caucasian	Not stated, range 25-85	Inpatients, Scr 1-1.4, CrCl 37-115	Cross Sectional	24 hour urine creatinine clearance
Walser, Drew, Guldan	85 (54, 31)	Not stated, range 23-79	Outpatients with CRI, average GFR 13	Cross Sectional	99cTM-DTPA
Toto, Kirk, et al	193 (76% male) 100% African American	53 (23-70)	Outpatients with GFR 25-75	Cross Sectional	Iothalamate

**The correction of 15% for women in Cockroft and Gault's study is based on two previous studies, one based on life insurance data and another with an N of 17*

Estimations of GFR from serum creatinine

- Cockroft-Gault: $\frac{((140 - age) \times weight(kg, IBW))}{72 \times serumCr(mg/dl)}$

(Multiply by 0.85 for women)

- Walser-Drew-Guldan:
  - Males:

$$\frac{7.57}{Scr(mmol/L)} - 0.103 \times age + 0.096 \times weight(kg) - 6.66$$

  - Females:

$$\frac{6.05}{SCr(mmol/L)} - 0.08 \times age + 0.08 \times weight(kg) - 4.81$$

Estimations of GFR from serum creatinine

- Toto, Kirk et al:
  - 100/Scr (mg/dl) or
  - Men: -0.3*(Age-52)+(105/Scr)+(Weight-86)
  - Women: -.29*(Age-52)+(88/Scr)-0.77*(BMI-30)
    - In men, use of weight in the regression equation was more predictive of GFR than BMI; the reverse was true for women.

Summary

- Creatinine clearance has never provided a better estimate of GFR than serum creatinine in CRF (1)
- Estimating GFR from serum creatinine when serum creatinine is elevated is very important.
- All the major formulas listed previously include Age, gender and either height or weight as variables. Race has not adequately been factored in all except the Toto equation.

Summary (Cont'd)

- The most valid equations for use in chronic renal failure are the Walser-Drew-Guldan equation, and if adjusting for race, the equation of Toto et al.
- However, HCFA currently only accepts serum creatinine, the Cockroft-Gault equation, creatinine clearance, or an average of the creatinine and urea clearance for determining eligibility for dialysis initiation.

Summary (Cont'd)

- These equations need to be acknowledged by regulatory agencies as appropriate indicators of GFR and therefore as reliable indications for end stage renal disease treatment.
- A tool exists for plotting serial CrCl or GFR's over time and estimating the timing for dialysis (this tool can also be used to estimate timing of access placement, or referral to multidisciplinary ESRD clinics)

Conclusions

- Recall limitations of serum creatinine as a marker for GFR
- Know radioisotope markers for GFR
- Know use of cimetidine for estimating GFR
- Know the best formulas to estimate GFR in CRF, and tools incorporating them.